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A formal synthesis of martinelline via a combination of two types of radical reactions

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Abstract—A formal synthesis of martinelline has been accomplished via two types of radical reactions as the key steps. These are the radical addition–cyclization–elimination of an oxime ether carrying an unsaturated ester and a C–C bond formation through a radical 1,5-hydrogen atom translocation.

Martinelline and martinellic acid were isolated from an organic extract of the *Martinella iquitosensis* root in 1995.[1] These compounds show antibiotic activity against Gram-positive and Gram-negative bacteria, affinity for several G-protein receptors, and are the first nonpeptide bradykinin receptor antagonist reported to date. The pyrrolo[3,2-*c*]quinoline ring system of the martinellines core has not been reported previously in any natural product. Their biological activity and unique structure have made them the subject of intense synthetic interest (Fig. 1).[2–11]

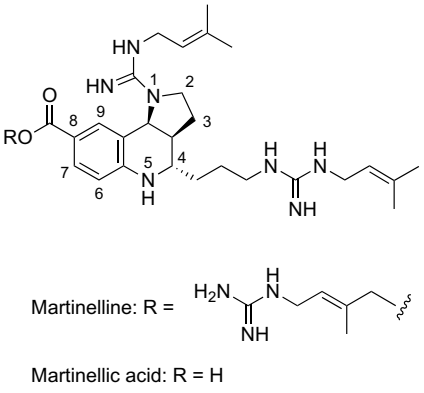

Figure 1.

As part of our program on radical addition–cyclization of oxime ethers connected with α,β-unsaturated carbonyl group,[12] we focused our efforts upon a synthesis of martinelline and designed our strategy leading to a key intermediate **18** for the synthesis of martinelline.[9b] Our synthetic strategy includes two crucial radical reactions; (1) a newly-found radical addition–cyclization–elimination of an oxime ether carrying an unsaturated ester for the construction of the pyrroloquinoline; (2) C–C bond formation through a 1,5-hydrogen atom translocation[13] for the stereoselective introduction of the side chain into the C(4) position of pyrroloquinoline (Scheme 1).

We first investigated the radical addition–cyclization of an oxime ether carrying an unsaturated ester **1** and found an interesting radical addition–cyclization–elimination, which has provided a novel and efficient method for the construction of the pyrroloquinoline. Requisite oxime ether **1** was readily prepared from commercially available methyl anthranilate **5**. N-Tosylation of **5** gave **6** in 68% yield, which was reduced with $LiAlH_4$ and then oxidized with MnO_2 to afford aldehyde **8**. Condensation of aldehyde **8** with *O*-benzylhydroxylamine hydrochloride in the presence of AcONa gave oxime ether **9** in 80% yield (three steps from **6**), which was then N-alkylated with ethyl 4-bromocrotonate to afford **1** in 95% yield.

According to our procedure developed in the radical addition–cyclization of oxime ethers,[12] treatment of

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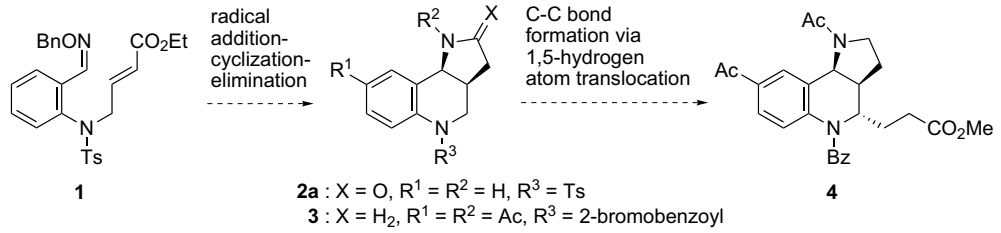
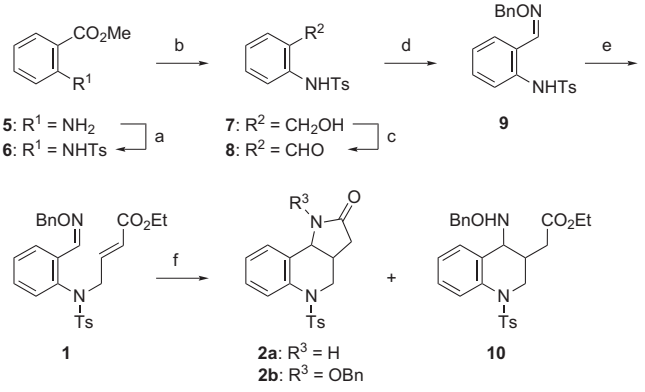


Scheme 1.

oxime ether **1** with Bu_3SnH and AIBN in refluxing benzene gave two types of products **2a** and **10**. Surprisingly, a major product of the reaction was an unexpected tricyclic pyrroloquinoline **2a**, which does not have the benzyloxy group (52%, *cis*/*trans* = 1:1) in the molecule. The minor product was an expected bicyclic tetrahydroquinoline **10** (22%, *cis*/*trans* = 1:1.5). The structures of *cis*-**2a** and *trans*-**2a** were deduced from their spectral data.[14] The debenzyloxylated major product **2a** would be formed as a result of stannyl radical addition–cyclization–elimination accompanied with debenzyloxylation. In order to propose a reaction pathway from **1** to **2a**, we examined the interconversion of the products. When *cis*-**10** was further treated with Bu_3SnH and AIBN, most of the starting material was recovered. Heating of *cis*-**10** in MeOH in the presence of TsOH gave cyclized *N*-benzyloxy *cis*-**2b**, which however was not converted into *cis*-**2a** under the same conditions for the radical reaction. When heated in MeOH in the presence of TsOH or under radical reaction conditions, *trans*-**10** was completely recovered. The reaction pathway of the radical addition–cyclization–elimination is ambiguous at the moment (Scheme 2).

We next examined the introduction of a carbonyl group into the C(8) position and a C_3 unit into the C(4) position of *cis*-**2a** possessing requisite stereostructure for the synthesis of martinelline. Reduction of *cis*-**2a** with $BH_3{\cdot}Me_2S$ followed by workup with 6 M HCl to cleave the B–N bond of the resulting intermediate gave the corresponding amine, which was then acetylated with

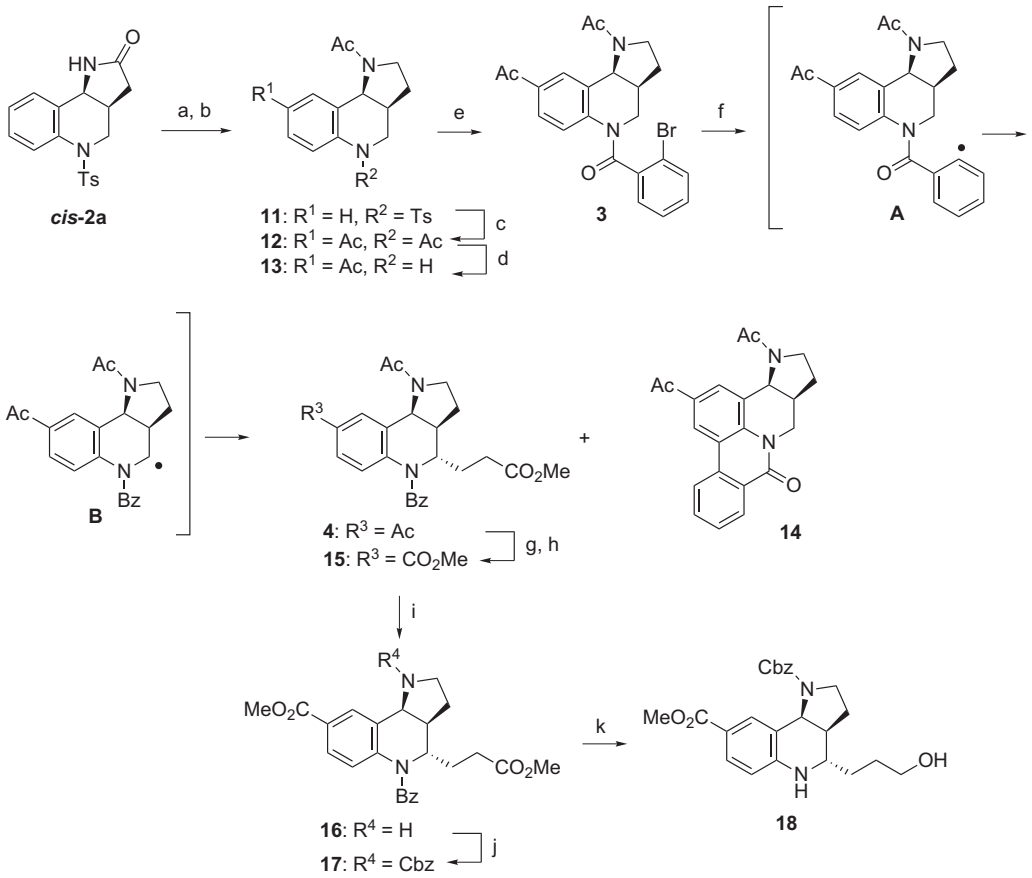


Scheme 2. Reagents and conditions: (a) TsCl, Et_3N, CH_2Cl_2, rt; (b) $LiAlH_4$, THF, 0 °C; (c) MnO_2, CH_2Cl_2, rt; (d) $BnONH_2{\cdot}HCl$, AcONa, MeOH–CH_2Cl_2, rt; (e) ethyl 4-bromocrotonate, K_2CO_3, acetone, rt; (f) Bu_3SnH, AlBN, benzene, reflux.

AcCl in the presence of Et_3N to give amide **11** in 90% yield (two steps from *cis*-**2a**). According to the known procedure,[15] we investigated the Friedel–Crafts reaction of **11**. When **11** was treated with AcCl (3 equiv) and $AlCl_3$ (6 equiv) in refluxing 1,2-dichloroethane, we obtained fortunately the 1,5,8-triacetyl compound **12** in which the tosyl group was converted into the easily removable acetyl group.[16] Treatment of **12** with 10% aq NaOH in MeOH at room temperature caused selective deacetylation at the vinylogous imide system to give the 1,8-diacetyl compound **13** in 47% yield (two steps from **11**).

Snieckus and co-workers[13e] have reported a diastereoselective carbon–carbon bond formation of an α-carbon adjacent to a nitrogen via a 1,5-hydrogen atom translocation and subsequent Michael-type radical addition to methyl acrylate. This method would allow the introduction of the C_3 unit side chain into the C(4) position adjacent to nitrogen from the less hindered convex face to afford the desired product. Amine **13** was acylated with 2-bromobenzoyl chloride in the presence of Et_3N to give the radical precursor **3** in 91% yield. When a solution of Bu_3SnH and AIBN in benzene was slowly added to a solution of **3** and methyl acrylate in refluxing benzene using a syringe pump, the desired compound **4** was formed as a single diastereomer in 43% yield along with the pentacyclic product **14** (19%). Formation of **14** would involve radical cyclization of the transiently formed aryl radical **A** onto the aromatic ring followed by oxidation. The conversion of the C(8)-acetyl group into the methoxycarbonyl group in **4** was achieved by the conventional procedure using haloform reaction. Treatment of **4** with Br_2 in 2.5% aq NaOH followed by esterification of the resulting carboxylic acid gave ester **15** in 76% yield (Scheme 3).

In order to convert **15** into the known intermediate **18** for martinelline synthesis, we investigated the conversion of functional groups. Treatment of **15** with $Et_3O{\cdot}BF_4$ followed by hydrolysis of the resulting imidate with saturated aq $NaHCO_3$ afforded amine **16** in 40% yield along with starting material **15** (32%). Amine **16** was reacted with CbzCl in the presence of Et_3N to give the protected compound **17** in 76% yield. Finally, the regioselective reduction of the isolated ester moiety in **17** with $LiBH_4$ in a mixture of 1/10 MeOH–THF at room temperature gave the desired alcohol **18**, which is a key intermediate for the synthesis of martinelline. The spectra of **18** were superimposable with those provided by Professor Ma.[9b]



Scheme 3. Reagents and conditions: (a) $BH_3{\cdot}Me_2S$, THF, reflux; (b) AcCl, Et_3N, CH_2Cl_2, 0 °C; (c) AcCl, $AlCl_3$, $ClCH_2CH_2Cl$, reflux; (d) 10% NaOH, MeOH, rt; (e) 2-bromobenzoyl chloride, Et_3N, CH_2Cl_2, rt; (f) methyl acrylate, Bu_3SnH, AIBN, benzene, reflux; (g) Br_2, 2.5% NaOH, 0 °C; (h) concd H_2SO_4, MeOH, reflux; (i) $Et_3O{\cdot}BF_4$, $NaHCO_3$, rt, then satd $NaHCO_3$, rt; (j) CbzCl, Et_3N, CH_2Cl_2, 0 °C; (k) $LiBH_4$, MeOH–THF, rt.

In conclusion, we have developed a novel and efficient strategy for the synthesis of pyrroloquinoline and succeeded in a formal synthesis of martinelline via the route involving two radical reactions of which the newly-found radical addition–cyclization–elimination constructed the martinelline skeleton in one procedure.

Acknowledgements

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14. *cis*-**2a**: IR ν_{max} cm^{-1} ($CHCl_3$): 3433, 1701, 1354, 1166. ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.02 (1H, dd, $J = 17.5$, 2 Hz), 2.40 (3H, s), 2.54 (1H, m), 2.62 (1H, dd, $J = 17.5$, 9 Hz), 3.15 (1H, dd, $J = 14$, 12 Hz), 4.20 (1H, dd, $J = 14$, 5 Hz), 4.37 (1H, d, $J = 6.5$ Hz), 6.60 (1H, br s), 7.16–7.28 (4H, m), 7.31 (1H, td, $J = 7.5$, 1 Hz), 7.52 (2H, br d, $J = 8$ Hz), 7.71 (1H, dd, $J = 8$, 1 Hz). HRMS *m/z*: calcd $C_{18}H_{18}N_2O_3S$ (M^+) 342.1037. Found: 342.1042. *trans*-**2a**: IR ν_{max} cm^{-1} ($CHCl_3$): 3429, 1727, 1356, 1168. ^1H NMR ($CDCl_3$, 500 MHz) δ: 2.10 (1H, m), 2.20 (1H, dd, $J = 15.5$, 12.5 Hz), 2.39 (3H, s), 2.55 (1H, dd, $J = 15.5$, 6.5 Hz), 3.23 (1H, d, $J = 10.5$ Hz), 3.58 (1H, br t, $J = 11$ Hz), 3.99 (1H, dd, $J = 11$, 6 Hz), 6.99 (1H, br d, $J = 7.5$ Hz), 7.17–7.21 (3H, m), 7.30–7.35 (1H, br t, $J = 8$ Hz), 7.40–7.46 (3H, m), 7.82 (1H, dd, $J = 8$, 0.5 Hz). HRMS *m/z*: calcd $C_{18}H_{18}N_2O_3S$ (M^+) 342.1037. Found: 342.1047. The stereostructures of *cis*-**2a** and *trans*-**2a** were deduced on the basis of their *J* values of 9b-H (6.5 Hz for *cis*-**2a** and 10.5 Hz for *trans*-**2a**) and confirmed by chemical conversion of *cis*-**2a** into the known intermediate **18**.[9b]
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